REMARKS

This submission is in response to the non-final Office Action mailed March 5, 2007. Claims 1-23 were previously pending. Claim 3 has been canceled without prejudice or disclaimer. Claims 18 and 19 have been withdrawn by the Examiner. Accordingly, claims 1, 2, 4-17 and 20-23 are now pending and at issue.

Independent claims 1 and 21 have been amended to recite morphine base monohydrate instead of a pharmaceutically active agent. Support for this amendment can be found, for example, in claim 6 as originally filed. Claims 2, 4-6, 20 and 22 have been amended to refer to morphine base monohydrate.

Claims 1 and 21 have been amended to recite "to provide substantially linear absorption rates upon administration" in the body of the claim. Claim 21 has been amended to recite "wherein the molecule to molecule ratio of morphine base monohydrate to the controlled release chitosan polymer ranges from about 1:1 to about 100,000:1." Support for these amendments can be found, for example in the claims as originally filed, on page 16, lines 10-12 and Figures 1 and 2. Claims 1 and 21 have also been amended to remove the word "aqueous" from the preamble. Claim 15 has been amended to refer to claim 1 instead of claim 12.

Applicants request reconsideration of this application in view of these amendments and the remarks below.

Amendments to the Specification

Through error and without deceptive intent, applicants referred to the linear uptake of active ingredient as first order rate kinetics (see, for example, page 7, lines 14-18). Linear uptake

of an active ingredient, however, demonstrates zero-order rate kinetics (see, e.g., U.S. Patent No. 4,361,545, col. 15, lines 11-13; U.S. Patent No. 6,296,873, col. 3, lines 51-56; U.S. Published Application No. 20030104062, paragraphs 39 and 51). Applicants have amended the specification to correct this obvious error.

Linear absorption of active ingredient was disclosed in the application as-filed (see Figures 1 and 2, which demonstrate substantially linear uptake of morphine). A person of ordinary skill would characterize linear absorption as zero order rate kinetics, not first order rate kinetics. Accordingly, no new matter has been added by this amendment (see MPEP § 2163.07 II, "An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction.")

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1-17 and 20-23 stand rejected as indefinite. The Examiner states that it is unclear how the composition can be aqueous when water is an optional component. Claims 1 and 21 have been amended to remove the word "aqueous" in the preamble. Applicants request that this rejection be withdrawn.

The Examiner asserts that the terms "therapeutically effective" and "an effective amount" are unclear, and that it is unclear exactly how much is effective and what the desired effect actually is. (Claims 1 and 21 (as amended) recite "a therapeutically effective amount of morphine base monohydrate" and "an effective amount of a controlled release chitosan polymer".)

A therapeutically effective amount of morphine base monohydrate is an amount that is effective for the purpose for which the morphine is administered, and can be determined by a person of ordinary skill in the art in view of, for example, the potency of the morphine base monohydrate, the route of administration and the mechanical system used to administer the formulation (see page 9, lines 1-6 of the application as filed).

An effective amount of a controlled release chitosan polymer is also definite, and is understood by persons of ordinary skill in the art. It refers to an amount of chitosan polymer that produces a controlled increase in plasma levels of morphine (or plasma levels of morphine metabolites) during the absorption phase after nasal administration (see page 7, lines 8-10 of the application as filed). A controlled increase in plasma levels of morphine is a morphine dosage that provides substantially linear uptake (see page 7, lines 17-18 of the application as filed).

Because the terms "therapeutically effective" and "an effective amount" would be understood by a person of ordinary skill in the art, applicants request that the indefiniteness rejections be withdrawn.

The Examiner alleges that there is insufficient antecedent basis for the limitation "antimicrobial agent" in claims 14-15. Antecedent basis for the term "antimicrobial agent" is provided by claim 1, from which claims 14-15 indirectly depend. Applicants do note, however, that claims 14 and 15 as-filed have the same scope. Claim 15 has been amended to depend from claim 1 instead of claim 12.

Rejections Under 35 U.S.C. § 103

Claims 1-17 and 21-23 stand rejected as obvious over Illum et al. (U.S. Patent No. 6,387,917). The Examiner states that Illum discloses a composition of methane sulphonate salt that is combined with chitosan to provide an increased absorption of the drug and asserts that Examples 2 and 3 disclose a solution for intranasal administration comprising morphine base (monohydrate) and chitosan.

The morphine base monohydrate in Example 2 of Ilum is converted to the methane sulphonate salt of morphine upon the addition of 2M methane sulphonic acid (see Ilum, col. 5, lines 45-49). This occurs prior to the addition of the chitosan solution. Example 3 also does not employ morphine base monohydrate; morphine hydrochloride is used instead (see Ilum, col. 5, lines 66-67). Accordingly, applicants respectfully disagree with the Examiner's assertion that Examples 2 and 3 disclose solutions containing morphine base monohydrate and chitosan. To advance prosecution, claims 1 and 21 have been amended to recite morphine base monohydrate as the pharmaceutically active ingredient.

The Examiner states that the instant claims differ in the specified percentages selected for the compositions. Nevertheless, the Examiner asserts that:

> It would have been deemed *prima facie* obvious . . . to optimize the percentage of active ingredient and the controlled release polymer to prepare a composition containing a therapeutically effective amount of active agent because the determination of a specific percentage having optimal therapeutic effect is well within the level of one having ordinary skill in the art, and the artisan

> would be motivated to determine optimum amounts to get the maximum effect of the active compounds.

(March 5, 2007 Office Action, page 12, first full paragraph) The Examiner concludes that the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicants respectfully disagree with the Examiner's assertion that selection of the instantly claimed morphine base monohydrate:controlled release chitosan ratio is mere optimization. One cannot optimize a variable without awareness of the result for which the variable is optimized. Illum does not disclose or suggest *the possibility* that a molecular ratio of morphine base monohydrate to chitosan polymer can be selected to obtain a controlled release formulation of morphine base monohydrate (i.e., to provide a substantially linear uptake of morphine). Accordingly, it is unfair to suggest that mere optimization of this previously un-emphasized ratio could lead to the presently claimed controlled release formulation when it was not known that controlled release of morphine was possible upon combining chitosan and morphine base monohydrate at the ratios recited in claim 1.

The present application recognizes that chitosan was previously known to increase the residence time of orally or nasally administered drugs to mucosal membranes (and hence promote absorption) based on its mucoadhesive properties (see present application, page 20, lines 19-29). What is surprising, however, and unrecognized by Illum is that specific amounts of chitosan and morphine base monohydrate also provide controlled-release morphine compositions when transmucosally administered, i.e., provide substantially linear absorption rates upon administration. This is a surprising result; one would not envision, for example, a linear absorption profile of morphine based only on increased residence time on a mucosal membrane.

The addition of chitosan in specified amounts to transmucosal formulations containing morphine yields an improvement (controlled release of morphine) that is much more than the predictable use of chitosan according to its previously established function as a mucoadhesive. *Cf. KSR International v. Teleflex Inc.,* 550 U.S. _____ (2007), slip opinion at page 13 ("a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions").

Independent claims 1 and 21 recite a specific ratio of morphine base monohydrate:chitosan which produces controlled release of morphine (see page 6, lines 23-29 of the application as filed). The instantly claimed ranges of morphine base monohydrate:chitosan would not have been obtained through mere optimization of the compositions disclosed in Ilum, as Illum does not recognize that chitosan can be used to provide controlled release formulations of morphine base monohydrate. Accordingly, applicants request that the obviousness rejection be withdrawn.

To further distinguish the claims of the present application from the prior art, claims 1 and 21 have been amended to recite "to provide substantially linear absorption rates upon administration". As discussed above, Illum does not teach or suggest this limitation.

Claims 1-5, 7-8, 16-17 and 21-22 stand rejected as obvious over Illum II (U.S. Patent No. 5,629,011). Claims 1-5, 7-12, 16-17 20-21 and 23 stand rejected as obvious over Hansen (U.S. Patent No. 5,955,502). Claims 1-5, 7-17 and 20-21 stand rejected as obvious over Dellamary (U.S. Patent No. 6,433,040).

Claim 6, which recited purified morphine base monohydrate does not stand rejected by these references. Illum II discloses polar metabolites of analgesics, such as morphine-6-glucuronide and morphine-6-sulphate. Hansen and Dellamary disclose a laundry list of active

agents that includes morphine, but neither reference discloses or suggests that the recited ratio of morphine base monohydrate to chitosan yields substantially linear absorption rates upon administration.

As claims 1 and 21 have been amended to recite morphine base monohydrate, and Illum II, Hansen or Dellamary do not disclose or suggest sustained release compositions that include the recited ratio of morphine base monohydrate to chitosan to provide substantially linear absorption rates upon administration, applicants request that the obviousness rejection be withdrawn.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be considered for substantive examination. If there are any other issues remaining which the Examiner believes could be resolved either through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below. Applicants believe no fee is due at this time. However, if any fees are required, the Commissioner is authorized to charge such fee to Deposit Account No. 02-4377.

Dated: August 28, 2007

Respectfully submitted,

By _____
Jason C. Chumney
Registration No.: 54,781

Baker Botts L.L.P.
30 Rockefeller Plaza
44th Floor
New York, NY 10112-4498
(212) 408-2500
(212) 408-2501 (fax)

Attorneys/Agents For Applicant